



Maternal Health Task Force



Syphilis in Pregnancy

The Geneva Foundation for Medical Education and Research

On successful completion of this module you should describe and explain:

- The natural course of syphilis.
- The public health challenges posed by syphilis.
- Classification of congenital syphilis (MTCT of syphilis).
- The global burden of the mother-to-child transmission (MTCT) of syphilis.
- Risk factors for MTCT of syphilis.
- Strategies and standards to reduce the risk of MTCT of syphilis.
- Recommended tests for the diagnosis and screening of syphilis.
- Medicines used to reduce the risk of MTCT of syphilis.
- Medicines used for congenital syphilis treatment.

Definition

Syphilis is a systemic human disease caused by *Treponema pallidum*, subspecies *pallidum* (*T. pallidum*).

Classification

- Acquired (usually by sexual contact or through blood transfusion).
 - Early (includes: primary, secondary and early latent syphilis).
 - Late (includes: latent and tertiary gummatous, cardiovascular and neurosyphilis).
- Congenital (transmitted from mother to child in utero).
 - Early (first 2 years).
 - Late, including stigmata of congenital syphilis.

Syphilis has three clinical stages:

The primary stage - the infected person develops a painless ulcer (most often in the anogenital region, can be in mouth or rectum) – called a chancre (starts 21 days (range: 10–90 days) following infection, lasts 2–6 weeks). (WHO 2007)

The secondary stage - is characterized by a skin rash over the whole body, often with fever and muscle pain (starts 2 – 3 months after onset of chancre, lasts 2–6 weeks). Followed by a latent phase of many years with no signs or symptoms. (WHO 2007)

Latent syphilis – is a period after infection during which patients are seropositive but have no clinical manifestations of disease.

- Early latent is when infection was acquired within preceding year.
- Late latent syphilis includes all other cases. (PAHO 2008)

The tertiary stage - takes the form of neurosyphilis, cardiovascular syphilis, or late benign syphilis (occurs several years to several decades after infection).(WHO 2007)

Diagnosis: clinical

- Definition of stages is clinical, chronology begins with the onset of a chancre. (Janier 2014)
- Stages could be overlapping. (Janier 2014)
- Secondary syphilis develops in one-third of untreated patients, tertiary syphilis in 10%. (Janier 2014)
- Patients are considered infectious to others through sexual contact and rarely social contact during the first year (primary and secondary syphilis). (Janier 2014)
- Syphilis spreads from person to person via skin or mucous membrane contact with an active chancre/sore. Infected person can transmit syphilis through infected blood products (blood transfusion or use of infected needles) (Tayou 2011)
- After the first year transmission is possible through tissue donation or vertically. (Janier 2014)

Incubation period:

- 10 –90 days between contact (mostly sexual) and a chancre.(Janier 2014)

Janier M, Hegyi V, Dupin N, Unemo M, Tiplica GS, Potočnik M, French P, Patel R. 2014 European guideline on the management of syphilis. J Eur Acad Dermatol Venereol. 2014 Dec;28(12):1581–93.

Tayou C. Syphilis and Blood Safety in Developing Countries. In: Sato NS, ed. Syphilis - Recognition, Description and Diagnosis. InTech; 2011 Nov 21.

Primary syphilis

The primary stage usually begins 21 days (range: 10-90 days) following infection and lasts 2–6 weeks. (PAHO 2008)

First, clinical manifestation is usually a local lesion at the site of entry of the bacteria, that appears as a single, firm, round, painless red sore, called a chancre, and enlarged lymph nodes around the area where there has been sexual contact. (PAHO 2008)

Many primary infections are asymptomatic and signs of infection are missed because the chancre may be hidden in the vagina, cervix or oropharynx. This infective chancre heals after 4-6 weeks. (PAHO 2008)

Any ulcer in an anogenital area should be suspected as syphilis until it is confirmed or rejected by diagnostic and laboratory tests. Initial tests may not allow a firm and conclusive rejection of a syphilis diagnosis and retesting with serology at 1, 2 and 6 weeks is needed to exclude a diagnosis (Janier M 2014).

Secondary syphilis

Secondary syphilis begins 1 to 2 months later (Janier 2014).

In untreated cases it manifests with:

Maculopapular, polymorphic and generalized skin rash, mostly on palms and soles. Skin rash can also occur in areas around the vulva and anus. Skin rash is not itchy or painful.(PAHO 2008)

Other clinical manifestations include generalized lymphadenopathies, malaise, fever, splenomegaly, sore throat, headache and arthritis.(PAHO 2008)

Secondary phase of syphilis disappears spontaneously with time. In the first years of its latency, the infective lesions of the skin and mucous membranes can recur. (PAHO 2008)

Fever, generalized lymphadenopathy, hepatitis, splenomegaly, periostitis, arthritis and glomerulonephritis are possible. (Janier 2014)

This stage lasts 2–6 weeks. (Janier 2014)

Latent, tertiary syphilis and neurosyphilis

If not treated, around one-third of secondary syphilis cases will remain latent for weeks and even years. (PAHO 2008)

If not treated, the clinical manifestations of the tertiary stage of syphilis can reappear even after many years, and affect the brain, nerves, eyes, large blood vessels, the heart, skin, joints and bones. (PAHO 2008)

Neurosyphilis occurs when the infection extends to the central nervous system. (Janier 2014)

Neurosyphilis can occur in any stage of the infection. (Janier 2014)

Syphilis in pregnancy

- Manifestations of syphilis in pregnancy are the same as for non-pregnant women and syphilis may be acquired at any stage of pregnancy, whenever a pregnant woman is exposed.
- If a pregnant woman is infected, the *T. pallidum* organisms that enter her blood can be transmitted to the fetus.
- Transmission of *T. pallidum* to the fetus usually occurs between 16-28 weeks of pregnancy (but can happen as early as 9 weeks).
- The likelihood of transmission is directly related to the stage of syphilis in the infected pregnant woman. The concentration of spirochaetes in blood is highest in the primary and secondary stages of disease and decreases slowly thereafter (because of acquired immunity) .
- The course of maternal infection does not seem to be altered by pregnancy.

Risks associated with syphilis in pregnancy

- Syphilis in pregnancy can result in early fetal death, low birth weight, preterm delivery, neonatal death, infection or disease in newborn.

Mother-to-child transmission of syphilis: a continuing public health burden

Nearly 1.5 million pregnant women are infected with syphilis each year.

Approximately half of infected pregnant women who are untreated, will experience adverse outcomes due to syphilis.

Mother-to-child transmission (MTCT) of syphilis (commonly referred to as “congenital syphilis”) is relatively simple to eliminate but despite treatments that have been available for over 60 years, MTCT of syphilis persists as a public health problem.

Screening all pregnant women, using simple and low-cost technologies, and effective treatment with penicillin, is feasible, even in low-resource settings, but the exact proportion of pregnant women globally who receive adequate testing and treatment is unknown due to inadequate surveillance.

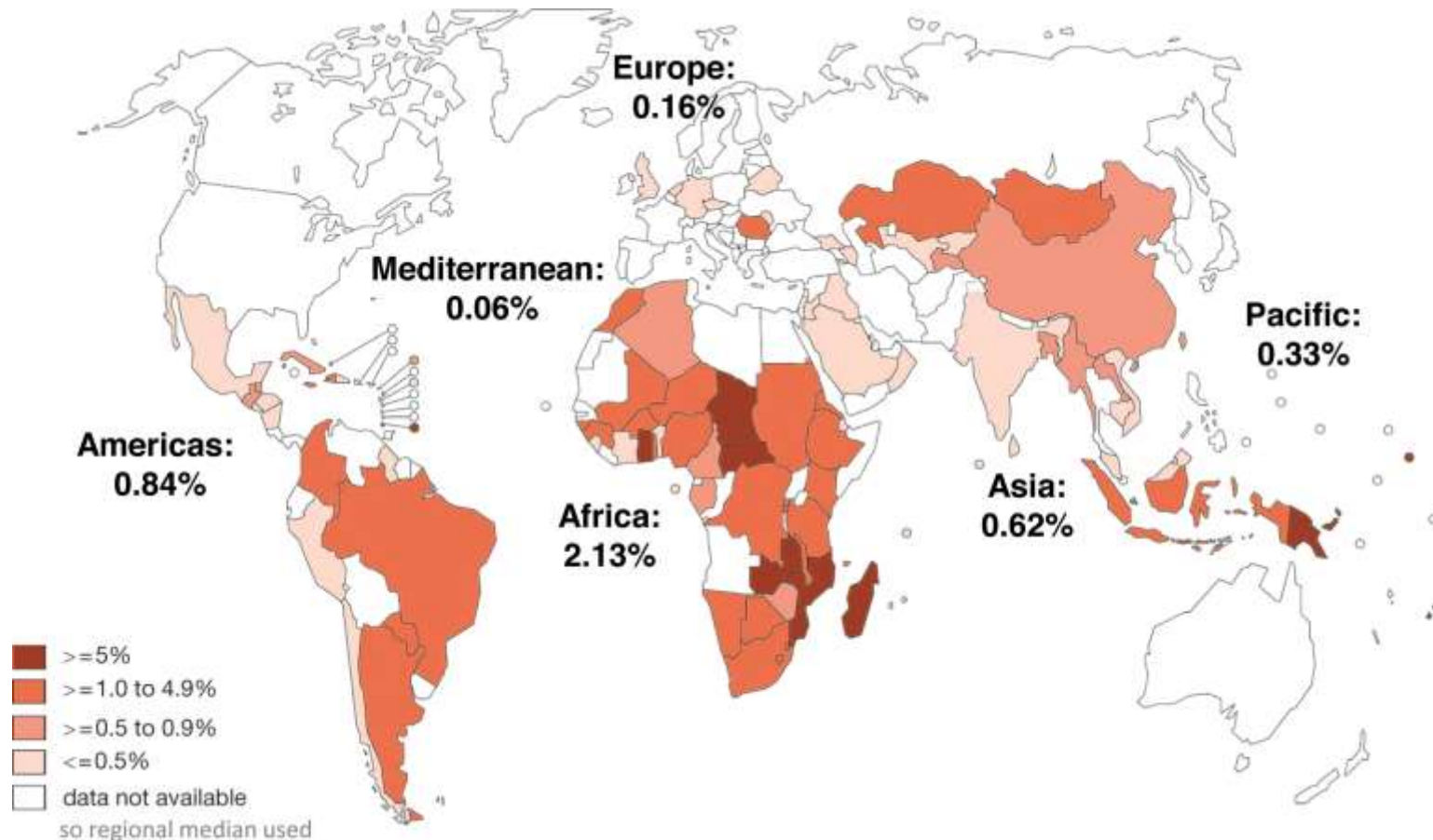
The World Health Organization (WHO) has started to monitor syphilis testing and treatment coverage through the HIV Universal Access reporting system, but quality data is not yet available from all countries.

Estimated percentage of adverse outcomes in untreated pregnancies affected by syphilis, and estimated number of adverse outcomes in 2008 taking into account existing services

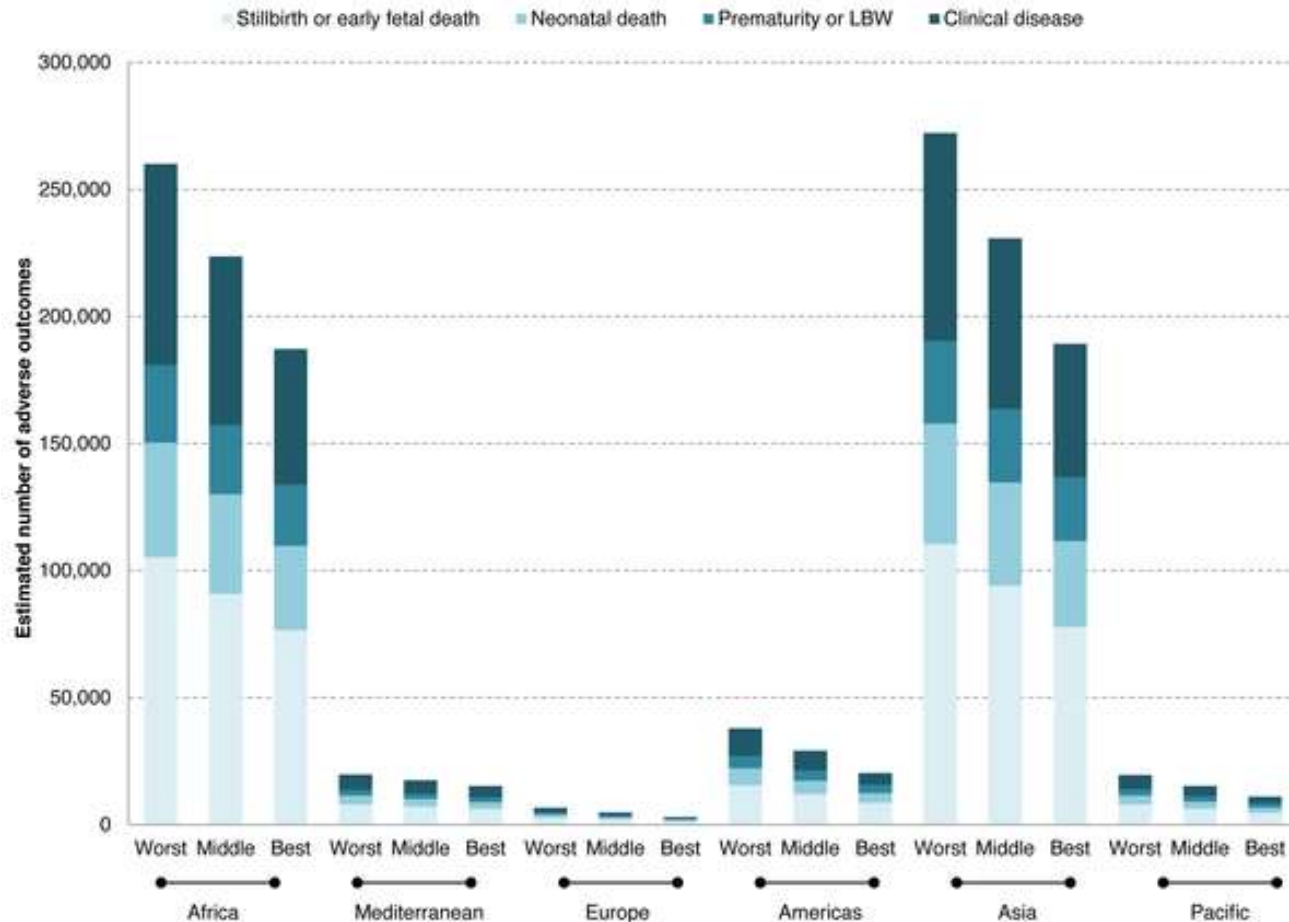
Outcome	Estimated % of adverse outcomes in untreated pregnancies affected by syphilis	Estimated number of adverse outcomes in 2008
Early fetal loss/stillbirth	21	215 000
Neonatal death	9	90 000
Prematurity or low birth weight	6	65 000
Clinical evidence of syphilis in newborn	16	150 000
Any adverse outcome	52	520 000

a Adverse outcomes estimates = % of pregnancies affected in syphilis seropositive women minus the % of pregnancies affected in syphilis seronegative women. This methodology thus accounts for background morbidity and mortality not attributable to syphilis.

Syphilis seropositivity among antenatal care attendees reported by countries through the WHO HIV Universal Access reporting system in 2008 or 2009, and regional median for non-reporting countries



Estimated number of adverse outcomes associated with syphilis in pregnancy in a worst, middle, and best case scenarios of testing and treatment in 2008 (LBW-low birth weight)



Estimates for MTCT of syphilis burden in 2008:

1,360,485 pregnant women with probable active syphilis infections (range 1,160,195–1,560,776)

Of these women, 1,085,637 (79.8%) attended ANC

The estimated number of infected pregnant women by region was:

- Africa: 535,203 (39.3%)
- The Americas: 106,500 (7.8%)
- Asia: 603,293 (44.3%)
- Europe: 21,602 (1.6%)
- The Mediterranean: 40,062 (3.0%)
- The Pacific: 53,825 (4.0%)

Is congenital syphilis still a global public health problem?

While substantial progress has been made in the utilization of ANC (in 2009 WHO estimated that approximately 81% of all pregnant women had attended at least one ANC visit), congenital syphilis still occurred for a variety of reasons:

- many of these visits were too late to avert an adverse outcome,
- clinics may not have offered testing,
- testing may not have been affordable,
- women may not have followed up or received their test results,
- treatment may not have been available,
- treated women may have been re-infected by untreated sexual partners.

Countries in every region of the world should scale up screening and treatment for syphilis in pregnancy to substantially reduce preventable perinatal death and disability.

Diagnosis and Screening

- Adverse pregnancy outcomes caused by untreated maternal syphilis are preventable and curable.(WHO 2012)
- Interventions to improve screening and treatment for syphilis in pregnancy can substantially reduce the current global burden of preventable perinatal mortality and morbidity.(WHO 2012)
- Screening of all pregnant women, using simple and low-cost technologies is feasible, even in low-resource settings.(WHO 2012)

Untreated early syphilis in pregnant women results in perinatal death in up to 40% of cases and, if acquired during the 4 years before pregnancy, can lead to infection of the fetus in 80% of cases. (CDC 2012)

Diagnosis and Screening

- **Non-treponemal screening tests** Venereal Disease Research Laboratory (VDRL) and the Rapid Plasma Reagin (RPR) test) detect antibody to reaginic antigen, which is found in both *T. pallidum* and some other conditions. They are thus **not specific for *T. pallidum***. (WHO 2007)
- False-positive non-treponemal test results can be associated with various medical conditions unrelated to syphilis, including autoimmune conditions, older age, and injection-drug use (198,199); therefore, persons with a reactive non-treponemal test should receive a treponemal test to confirm the diagnosis of syphilis. (CDC 2011)
- **If** a screening test is **positive**, the serum is then tested by **a confirmatory treponemal test**, using an antigen of *T. pallidum*, the *T. Pallidum* Haemagglutination Assay (TPHA) and the *T. Pallidum* Particle Agglutination Assay (TPPA). (WHO 2007)
- **Treponemal tests** are more specific than non-treponemal tests. But they **can not differentiate** between active **untreated** syphilis and successfully **treated** previous infection. (WHO 2007)
- **Non-treponemal tests** can **distinguish current** or recent infections **from old, treated** infections.
- A combination of the two types of tests is recommended in the sequence described above: screening followed by confirmation. (WHO 2007)

WHO indications for syphilis screening

- During pregnancy: all pregnant women at the first antenatal visit. Can be repeated in the 3rd trimester, to detect infection acquired during the pregnancy (**First priority should be to ensure universal antenatal screening**).
- At the time of delivery if no antenatal testing was done.
- With spontaneous abortion (miscarriage) or stillbirth.
- With diagnosis of other STI syndromes (screening for the pregnant woman and sexual partners).
- For sex workers - every 6 months.

WHO recommends that screening and treatment for syphilis should both be completed during the same patient encounter:

- Patients should receive their test results before leaving the clinic.
- Patients with reactive (positive) results should be treated immediately.
- All patients must be asked for a history of allergy to penicillin.
- Sex partners should also be treated.

Treatment of early syphilis (i.e. acquired ≤ 1 year previously) in pregnancy

First line therapy option

- Benzathine penicillin G (BPG) 2.4 million units IM single dose (or 1.2 million units in each buttock) [I; B]

Note: some specialists recommend two doses of BPG 2.4 million units (day 1 and 8) but there is not sufficient evidence to recommend this.

Patients should be kept for clinical observation (signs of allergic reaction) for 30 minutes after injection.

Second line therapy option

- Procaine penicillin 600 000 units IM daily for 10 – 14 days, i.e. if BPG is not available [III; B]

Pregnant women with penicillin allergy should be desensitized and treated with penicillin

Monitoring

If syphilis screening is already established in antenatal clinics, it should be monitored and reported the proportion of women who are tested, diagnosed and effectively treated.

Two simple indicators can be easily calculated each month from clinic records:

$$\text{Screening coverage} = \frac{\text{Number of pregnant women tested}}{\text{Number of women at first antenatal visit}}$$
$$\text{Treatment coverage} = \frac{\text{Number of RPR-reactive women treated}}{\text{Number RPR-reactive}}$$

MTCT of syphilis

- All asymptomatic infants born to seropositive women should receive at birth a prophylactic single dose of benzathine penicillin G (BPG), 50 000 IU/kg IM whether or not the mothers were treated during pregnancy (with or without penicillin).
- Diagnosis and treatment of congenital syphilis in infants are considerably more difficult than diagnosis and treatment of infected pregnant women.
- Newborn infants showing any clinical sign of congenital syphilis should be treated with benzyl penicillin or procaine for 10 days. Current treatment regimens for congenital syphilis involve administration of parenteral penicillin, and require hospitalization to ensure that the infant receives the full course of treatment.

Prevention of MTCT of syphilis by universal screening and treatment, if indicated, for women early in pregnancy, is more preferable than screening and treatment of infants postpartum.

MTCT of syphilis

- Syphilis test results should be reviewed at the time of labour, and the newborn evaluated for signs of congenital syphilis.
- Women who have not previously been tested for syphilis should be tested on admission for labor and birth.
- Results should be obtained as soon as possible so that early treatment can be given to newborns of mothers who test positive.
- Newborn babies should be managed as described, regardless of whether the mother received treatment for syphilis during pregnancy.
- The mother and her partner should also be treated if this has not already been done.

Congenital syphilis

Classification

- Confirmed congenital infection
- Presumed congenital infection
- Late congenital syphilis

Congenital syphilis

Confirmed congenital infection

T. pallidum demonstrated by Darkfield examination (DFE) or Polymerase chain reaction (PCR) in placenta or autopsy material, exudate from suspicious lesions or body fluids, e.g. nasal discharge.

Direct detection methods provide definitive diagnosis of syphilis.

- Darkfield examination (DFE) gives immediate results but the method is laborious, subjective and is subject to both false positive and (many) false negative results.
- Polymerase chain reaction (PCR) can be performed in tissues, cerebrospinal fluid (CSF), blood (although insensitive in the latter), etc. There is no internationally approved PCR for *T. pallidum* and accordingly, it is crucial to select a strictly validated method and always use it with appropriate quality controls.
- Algorithms for DFE and PCR for exact clinical situations are heavily dependent on local expertise and laboratory setups.

Congenital syphilis

Presumed congenital infection

- A stillborn neonate with a positive treponemal test for syphilis.
- Children with a positive treponemal test for syphilis in combination with one or several of the following:
 - persistent rhinitis, condylomata lata, osteitis, periostitis, osteochondritis, ascites, cutaneous and mucous membrane lesions, hepatitis, hepatosplenomegaly, glomerulo-nephritis, haemolytic anaemia;
 - radiological abnormalities of the long bones suggestive of congenital syphilis;
 - a positive RPR/VDRL test in the cerebrospinal fluid;
 - a fourfold increase or more of the TPPA/TPHA titre in the child's as opposed to the mother's serum (both obtained simultaneously at birth);
 - a fourfold increase or more of the titre of a non-treponemal test in the child's as opposed to the mother's serum (both obtained simultaneously at birth);
 - a fourfold increase or more of the titre of a non-treponemal test within 3 months after birth;
 - a positive anti-treponemal IgM EIA, 19S-IgM-FTA-abs test and/or IgM-immunoblot for *T. pallidum* in the child's serum;
 - a mother, in whom syphilis was confirmed during pregnancy, but who was not adequately treated either before or during pregnancy.
- In a child >12 months of age with a positive treponemal serologic test for syphilis and in whom sexual abuse has been excluded.

Congenital syphilis

Late congenital syphilis

- Interstitial keratitis, Clutton's joints, Hutchinson's incisors, mulberry molars, high palatal arch, rhagades, deafness, frontal bossing, short maxilla, protuberance of mandible, saddlenose deformity, sternoclavicular thickening, paroxysmal cold haemoglobinuria, neurological or gummatous involvement.
- Serological tests can be negative in infants infected in late pregnancy and should be repeated. When the mother is treated during the last trimester of pregnancy, the treatment can be inadequate for the child and the child may still develop congenital syphilis.
- All cases of congenital syphilis must be reported to the national Syphilis Surveillance system where required by local mandate.

Congenital syphilis: Investigation

- RPR/VDRL, TPPA/TPHA (quantitative), anti-treponemal IgM-EIA, treponemal IgM (19S-IgM FTA-abs or IgM-immunoblot) – from infant’s blood and not umbilical cord blood, because false-positive and false-negative tests may result.
- Blood: Full blood count, liver function, electrolytes.
- Cerebrospinal fluid (CSF): cells, protein, RPR/VDRL, TPHA/TPPA.
- X-rays long bones.
- Ophthalmic assessment as indicated.

Tools for the prevention and control of maternal and congenital syphilis

	Diagnosis/screening tests			Surveillance	
	Local	Regional laboratory	Reference laboratory	Sentinel site	Reference laboratory
Maternal syphilis					
Symptomatic	None	Dark-field microscopy, DFA-TP	Molecular tests such as PCR	Dark-field microscopy, DFA-TP	Molecular tests
Asymptomatic	RPR Rapid treponemal tests	RPR/VDRL EIA Rapid treponemal tests	RPR/VDRL EIA TPHA/TPPA FTA-ABS Immunoblotting	RPR/VDRL Rapid treponemal tests EIA	EIA TPHA/TPPA FTA-ABS
Congenital syphilis					
Symptomatic	None	Dark-field microscopy, DFA-TP	Molecular tests such as PCR	Dark-field microscopy, DFA-TP	Molecular tests
Asymptomatic	None	RPR/VDRL Ig M antibody detection by EIA	RPR/VDRL Ig M antibody detection by EIA	RPR/VDRL Rapid treponemal tests EIA	Ig M antibody detection by EIA

Congenital syphilis: Treatment

European Guideline recommendations (Jenier 2014)

First line therapy option

- Benzyl penicillin 150 000 units/kg IV daily (administered in six doses every 4 h) during 10–14 days [IV; C]
- If CSF is normal: check for age:
 - **First line therapy:** BPG 50 000 units/kg IM (single dose) up to the adult dose of 2.4 million units [IV; C]
 - **Second line therapy:** Procaine penicillin 50 000 units/kg IM daily for 10–14 days, i.e. if BPG is not available [IV; C]

WHO and CDC recommendations

Infants with signs of congenital syphilis

- Aqueous crystalline benzylpenicillin 100 000 - 150 000 units/kg daily (administered as 50 000 units/kg of body weight, IM or IV, every 12 hours during first 7 days of life and every 8 hours thereafter for a total of 10 days)

OR

- Procaine benzylpenicillin 50 000 units/kg IM daily for 10–14 days

Infants without signs of congenital syphilis

- Benzathine benzylpenicillin G 50 000 units/kg IM up to the adult dose of 2.4 million units in a single dose.
- (CDC 2011; WHO 2005).

Syphilis in HIV-infected patients

- Serological tests for syphilis in patients with HIV coinfection are generally reliable for the diagnosis of syphilis and for evaluation of treatment response.
- Patients with HIV coinfection may have a slower rate of decline of VDRL/RPR after treatment, which should not be considered as failure of response to treatment.
- In HIV-infected individuals with clinical suspicion of syphilis and negative syphilis serology (repeatedly), further investigations should be performed.
- The risk of neurological and ocular involvement due to early syphilis does not appear to increase in HIV-infected patients.
- Treatment of syphilis in patients with concomitant HIV infection is the same as non-HIV-infected patients, although there is very little data on the use of second line therapy options. Note: Careful follow-up is essential.

WHO standard for prevention of mother-to-child transmission of syphilis

All pregnant women should be screened for syphilis at the first antenatal care (ANC) visit within the first trimester and again in late pregnancy.

At delivery, women who for some reason do not have test results should be tested/retested.

Women testing positive should be treated and informed of the importance of being tested for HIV infection. Their partners should also be treated and plans should be made to treat their infants at birth.

Applying the WHO standard for prevention of MTCT of syphilis

1. Screen all pregnant women for syphilis with on-site rapid plasma reagin (RPR) or another rapid test at the first antenatal visit. Screening should be done preferably before 16 weeks of gestation to prevent congenital infection, and again in the third trimester.
2. Review syphilis test results at subsequent visits and at time of delivery. If the woman was not tested during pregnancy, syphilis screening should be offered after delivery.
3. Treat all seroreactive women with benzathine benzyl -penicillin at the recommended dosage of at least 2.4 million IU intramuscularly as a single dose, after having excluded allergy to penicillin. In the case of allergy to penicillin, the attendant should desensitize and treat with penicillin if trained to do so, or refer the patient to a higher level of care.
4. Advise women who test positive that their partner(s) must also be treated with the same regimen, as well as the baby as soon as possible after birth.
5. Advise women who test negative how to remain free from syphilis by promoting condom use during pregnancy.
6. Test for syphilis all women with a history of adverse pregnancy outcome (abortion, stillbirth, syphilitic infant, etc.) and treat accordingly.
7. Treat women with clinical disease or a history of exposure to a person with infectious syphilis.
8. Screen all women with syphilis for other sexually transmitted infections, including HIV, and provide counseling and treatment accordingly.
9. Offer voluntary counseling and testing of HIV to all women who screen positive for syphilis.
10. Make plans for treating the baby at birth.
11. Record testing results and treatment in the facility's logbook and the woman's ANC card.

WHO standard for preventive treatment and care of congenital syphilis in the newborn

All asymptomatic infants born to seropositive women should receive at birth a prophylactic single dose of benzathine penicillin.

Newborn infants showing any clinical sign of congenital syphilis should be treated with penicillin crystalline or procaine for 10 days.

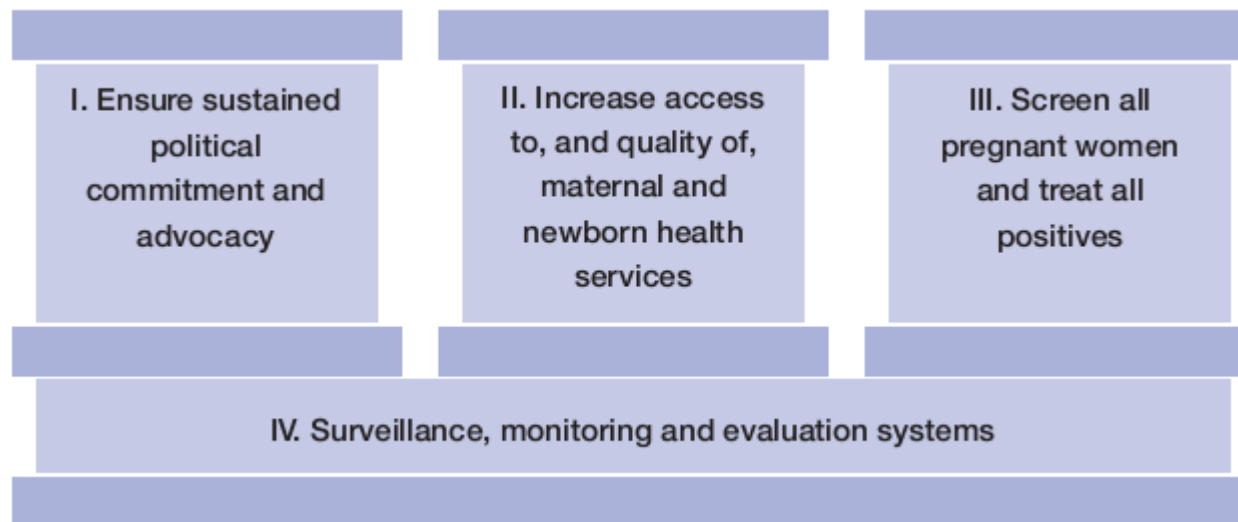
Any suspected case of congenital syphilis should be confirmed by testing the mother.

Applying the WHO standard for preventive treatment and care of congenital syphilis in the newborn

1. Check the antenatal care (ANC) card of all women giving birth and test and treat the woman as required (see standard on prevention of mother to child transmission of syphilis).
2. Examine carefully the newborn of any mother who tested positive for syphilis at any time during her pregnancy or at delivery to exclude signs of congenital syphilis.
3. Administer intramuscularly benzathine penicillin G 50 000 units/kg of body weight, single dose, to asymptomatic infants of women who have tested positive for syphilis.
4. In symptomatic babies confirm the diagnosis by testing the mother with a rapid test.
5. Administer intramuscularly the first dose of aqueous crystalline penicillin 50 000 units/kg of body weight or procaine penicillin G 50 000 units/kg of body weight intramuscularly to symptomatic babies whose mothers have tested positive for syphilis and refer them for treatment to a special care unit to receive 10 days of treatment.
6. Provide information to the woman on the importance of treating the newborn, herself and her partner
7. Provide information on STI prevention and on voluntary counselling and testing for HIV.
8. Record the treatment and the referral given on the ANC card and in the health facility logbook.

Initiative for the Global Elimination of Congenital Syphilis

In 2007, WHO launched its Initiative for the Global Elimination of Congenital Syphilis, with the goal that by 2015 at least 90% of pregnant women are tested for syphilis and at least 90% of seropositive pregnant women receive adequate treatment. Four public health “pillars” to eliminate perinatal syphilis were defined by WHO:



Methods for surveillance and monitoring of congenital syphilis elimination within existing systems. World Health Organization, 2011

STIs is still one of the global health sector strategies being planned for the post-2015 goals.

Millennium Development Goals 4, 5, 6

Elimination of MTCT of syphilis directly supports attainment of Millennium Development Goals 4, 5, and 6 through reduction in infant mortality, improved maternal health, and primary prevention of HIV.

MDG 4: reduce child mortality

MTCT of syphilis is a preventable cause of low birth weight, neonatal death, stillbirth and congenital infection.

MDG 5: improve maternal health

Providing more opportunities for women to be screened for syphilis and other conditions during pregnancy.

MDG 6: combat HIV/AIDS, malaria and other diseases

Syphilis infection is a recognized cofactor for increased risk of HIV transmission and acquisition, and maternal syphilis infection has even been associated with increased risk of MTCT of HIV. Systematic screening of women for syphilis in programmes for PMTCT of HIV will allow mothers and infants to be tested and, where necessary, treated for both HIV infection and syphilis, thereby reducing fetal and infant deaths.

As the world looks to 2030, and prepares to meet the challenges of an ambitious set of Sustainable Development Goals, the World Health Organization is developing three related global health sector strategies: HIV; viral hepatitis; and sexually transmitted infections (STIs), which contribute to future improvements in maternal and child health.

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